PA .NT COOPERATION TREAT .

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 December 2000 (14.12.00)	
International application No. PCT/EP00/03407	**Applicant's or agent's file reference** FC 859
International filing date (day/month/year) 14 April 2000 (14.04.00)	**Priority date** (day/month/year) 18 May 1999 (18.05.99)
Applicant DI SALLE, Enrico et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 November 2000 (23.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Nestor Santesso
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PHARMACIA & UPJOHN S.P.A
Viale Pasteur 1 o
I-20014 Nerviano
ITALIE

Date of mailing (day/month/year) 23 May 2000 (23.05.00)	
Applicant's or agent's file reference FC 859	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/03407	International filing date (day/month/year) 14 April 2000 (14.04.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 18 May 1999 (18.05.99)
Applicant PHARMACIA & UPJOHN S.P.A. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
18 May 1999 (18.05.99)	9911582.6	GB	04 May 2000 (04.05.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Aine Metcalfe

Telephone No. (41-22) 338.83.38

INT ATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03407

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.L. GREM E.A.: "A phase II evaluation of combination chemotherapy plus aminoglutethimide in women with metastatic or recurrent breast carcinoma" AMERICAN JOURNAL OF CLINICAL ONCOLOGY, vol. 11, no. 5, 1988, pages 528-528-534, XP000929348 page 528 -----	1-4, 10-15,21

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2000	08/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

1

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/EP 00/03407

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.L. GREM E.A.: "A phase II evaluation of combination chemotherapy plus aminoglutethimide in women with metastatic or recurrent breast carcinoma" AMERICAN JOURNAL OF CLINICAL ONCOLOGY, vol. 11, no. 5, 1988, pages 528-528-534, XP000929348 page 528 -----	1-4, 10-15,21

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2000	08/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

Form PCT/ISA/210 (second sheet) (July 1992)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:
PHARMACIA & UPJOHN S.P.A
Viale Pasteur 1 o
I-20014 Nerviano
ITALIE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 23 November 2000 (23.11.00)	
Applicant's or agent's file reference FC 859	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP00/03407	14 April 2000 (14.04.00)	18 May 1999 (18.05.99)

Applicant
PHARMACIA & UPJOHN S.P.A. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
   NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   23 November 2000 (23.11.00) under No. WO 00/69467

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
FC 859		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 03407	14/04/2000	18/05/1999
Applicant		
PHARMACIA & UPJOHN S.P.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03407

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.L. GREM E.A.: "A phase II evaluation of combination chemotherapy plus aminoglutethimide in women with metastatic or recurrent breast carcinoma" AMERICAN JOURNAL OF CLINICAL ONCOLOGY, vol. 11, no. 5, 1988, pages 528-528-534, XP000929348 page 528 -----	1-4, 10-15,21

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2000	08/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
FC 859		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 03407	14/04/2000	18/05/1999
Applicant		
PHARMACIA & UPJOHN S.P.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

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   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

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6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03407

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.L. GREM E.A.: "A phase II evaluation of combination chemotherapy plus aminoglutethimide in women with metastatic or recurrent breast carcinoma" AMERICAN JOURNAL OF CLINICAL ONCOLOGY, vol. 11, no. 5, 1988, pages 528-528-534, XP000929348 page 528 -----	1-4, 10-15,21

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2000	08/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Peeters, J

1

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FC 859		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03407	14/04/2000	18/05/1999
International Patent Classification (IPC) or national classification and IPC A61K45/06		
Applicant PHARMACIA & UPJOHN S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/11/2000	01.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Ludwig, G Telephone No. +49 89 2399 8698

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/03407

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-12	as originally filed

Claims, No.:

1-23	as received on	21/05/2001	with letter of	16/05/2001

Drawings, sheets:

1/1	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6, 18-19.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 6, 18 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-5, 7-17, 20-23

	No:	Claims	
Inventive step (IS)	Yes:	Claims	7
	No:	Claims	1-5, 8-17, 20-23
Industrial applicability (IA)	Yes:	Claims	1-5, 7-12 (13-17, 20-23 - cf. separate sheets)
	No:	Claims	

2. Citations and explanations
see separate sheet

D1: J.L. GREM E.A.: 'A phase II evaluation of combination chemotherapy plus aminoglutethimide in women with metastatic or recurrent breast carcinoma' AMERICAN JOURNAL OF CLINICAL ONCOLOGY, vol. 11, no. 5, 1988, pages 528-528-534, XP000929348

Item V:

1. The combined use of the antineoplastic combination scheme of cyclophosphamide, doxorubine (=adriamycin), and 5-fluorouracil (CAF) he aromatase inhibitor aminoglutheimide for use in breast cancer therapy is disclosed in document D1, a study carried out in humans.

2. The use of combination therapy is a well known approach for cancer treatment.

   For combinations of the aromatase inhibitor exemestane with the antineoplastic agents epirubicine (an anthracycline) and docetaxel (a taxane), respectively, a synergistic (superadditive) effect has been shown by the applicant in experiments with test animals (rats bearing DMBA-induced mammary tumours).

   Except for the class of anthracyclines and taxanes there appears to be no support in the description for the presence of a synergistic effect for rest of the antineoplastic agents, i.e. vinca alkaloids, alkylating agents, antimetabolites, and topoisomerase I inhibitors when used in combination with an aromatase inhibitor.

   Claims 1-5, 8-17, and 20-23 are therefore not regarded as inventive.

2.1 Novelty and inventive step appear to be present for claim 7.

3. For the assessment of the present claims 13-17, 20-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the

subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item III:

4. Claims 6 and 18 appear to extend beyond the content of the application as filed. A basis for these claims on page 6, lines 16-17 and 21-22 as indicated by the applicant could not be found.

5. Claims 13-17, 20-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FC 859		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03407	14/04/2000	18/05/1999
International Patent Classification (IPC) or national classification and IPC A61K45/06		
Applicant PHARMACIA & UPJOHN S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/11/2000	01.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Ludwig, G Telephone No. +49 89 2399 8698

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/03407

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-12	as originally filed				

Claims, No.:

1-23	as received on	21/05/2001	with letter of	16/05/2001	

Drawings, sheets:

1/1	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 6, 18-19.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 6, 18 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-5, 7-17, 20-23

	No:	Claims	
Inventive step (IS)	Yes:	Claims	7
	No:	Claims	1-5, 8-17, 20-23
Industrial applicability (IA)	Yes:	Claims	1-5, 7-12 (13-17, 20-23 - cf. separate sheets)
	No:	Claims	

2. Citations and explanations
see separate sheet

D1: J.L. GREM E.A.: 'A phase II evaluation of combination chemotherapy plus aminoglutethimide in women with metastatic or recurrent breast carcinoma' AMERICAN JOURNAL OF CLINICAL ONCOLOGY, vol. 11, no. 5, 1988, pages 528-528-534, XP000929348

Item V:

1. The combined use of the antineoplastic combination scheme of cyclophosphamide, doxorubine (=adriamycin), and 5-fluorouracil (CAF) he aromatase inhibitor aminoglutheimide for use in breast cancer therapy is disclosed in document D1, a study carried out in humans.

2. The use of combination therapy is a well known approach for cancer treatment.

   For combinations of the aromatase inhibitor exemestane with the antineoplastic agents epirubicine (an anthracycline) and docetaxel (a taxane), respectively, a synergistic (superadditive) effect has been shown by the applicant in experiments with test animals (rats bearing DMBA-induced mammary tumours).

   Except for the class of anthracyclines and taxanes there appears to be no support in the description for the presence of a synergistic effect for rest of the antineoplastic agents, i.e. vinca alkaloids, alkylating agents, antimetabolites, and topoisomerase I inhibitors when used in combination with an aromatase inhibitor.

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5. Claims 13-17, 20-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Claims

1. A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect, (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent, provided that when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

2. A composition according to claim 1, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite, and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

3. A composition according to claim 2. wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

4. A composition according to claim 3, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

5. A composition according to claim 3, wherein such a composition comprises 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole.

6. A composition according to claim 2, wherein the antineoplastic agent is selected from an anthracycline and a taxane compound and the steroidal aromatase inhibitor is exemestane.

7. A composition according to claim 5, wherein the composition comprises one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor is exemestane.

8. A composition, according to anyone of the preceding claims, wherein:

- the effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;
- the effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;
- the effective antineoplastic amount of mitoxantrone is from about 10mg/m^2 to about 20 mg/m^2;
- the effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;
- the effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;

- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;
- the effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1. mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

9. A composition according to claim 8, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.

10. A composition according to claim 8, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 50 to about 500 mg, and formestane is from about 250 to about 500 mg.

11. A product containing an antineoplastic agent and an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, for separate, simultaneous or sequential administration in breast cancer therapy in humans, and wherein when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

12. Use of an antineoplastic agent in the manufacture of a pharmaceutical composition for the treatment of breast cancer in a method additionally comprising the administration of an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, and wherein when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

13. A method for treating breast cancer in humans, the method comprising administering to a human in need thereof (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, provided that when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

14. A method, according to claim 13, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

15. A method according to claim 14, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

16. A method according to claim 15, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-

fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

17. A method according to claim 15, wherein 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole are administered.

18. A method according to claim 14, wherein the antineoplastic agent is selected from an anthracycline compound and a taxane compound and the steroidal aromatase inhibitor is exemestane.

19. A method according to claim 18, wherein one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor exemestane are administered.

20. A method according to claim 16 or 17, wherein:

- the effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;
- the effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;
- the effective antineoplastic amount of mitoxantrone is from about 10 mg/m^2 to 10 about 20 mg/m^2;
- the effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;
- the effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;

- the effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;
- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;
- the effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 30 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

21. A method according to claim 19, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.

22. A method according to claim 19, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 5 to about 500 mg, and formestane is from about 250 to about 500 mg.

23. A method for lowering the side effects in humans caused by breast cancer therapy with an antineoplastic agent, the method comprising administering to a human in need thereof a combined preparation comprising (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect, provided that when the antineoplastic agent is a combination consisting of

cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

AMENDED CLAIMS

[received by the International Bureau on 26 September 2000 (26.09.00);
original claims 1, 2, 10 – 13 and 21 amended; remaining claims unchanged (4 pages)]

1. A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect, (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent, provided that the aromatase inhibitor is not aminogluthetimide.

2. A composition according to claim 1, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

3. A composition according to claim 2, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

4. A composition according to claim 3, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

5. A composition according to claim 3, wherein such a composition comprises 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel,

about 1000 mg/m^2;

- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

8. A composition according to claim 7, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.

9. A composition according to claim 7, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 50 to about 500 mg, and formestane is from about 250 to about 500 mg.

10. A product containing an antineoplastic agent and an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, for separate, simultaneous or sequential administration in breast cancer therapy in humans, and wherein the aromatase inhibitor is not aminogluthetimide.

11. Use of an antineoplastic agent in the manufacture of a pharmaceutical composition for the treatment of breast cancer in a method additionally comprising the administration of an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, and wherein the aromatase inhibitor is not aminogluthetimide.

12. A method for treating breast cancer in humans, the method comprising administering to a human in need thereof (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, provided that the aromatase inhibitor is not aminogluthetimide.

13. A method, according to claim 12, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

14. A method according to claim 13, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

15. A method according to claim 14, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

16. A method according to claim 14, wherein 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole are administered.

1000 mg/m^2;

- the effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

19. A method according to claim 18, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.

20. A method according to claim 18, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 5 to about 500 mg, and formestane is from about 250 to about 500 mg.

21. A method for lowering the side effects in humans caused by breast cancer therapy with an antineoplastic agent, the method comprising administering to a human in need thereof a combined preparation comprising (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect, provided that the aromatase inhibitor is not aminogluthetimide.